

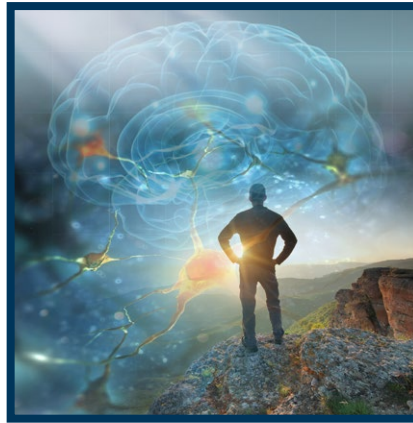
Environmental Risks for Psychiatric Disorders: Exploring Biological Mechanisms

March 21-22, 2017

Tuesday, March 21 • 9:00 a.m. – 4:40 p.m.

Wednesday, March 22 • 8:30 a.m. – 3:00 p.m.

Building 101, Rodbell Auditorium
Research Triangle Park, N.C.



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National Institutes of Health

U.S. Department of Health and Human Services

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Environmental Risks for Psychiatric Disorders: Exploring Biological Mechanisms



Welcome Message from Linda Birnbaum

On behalf of the National Institute of Environmental Health Sciences (NIEHS), I am honored and delighted to welcome you to the conference, “Environmental Risks for Psychiatric Disorders: Exploring Biological Mechanisms.”

Mental illness affects more than 43 million adults in the United States in a given year, with approximately half of all chronic mental illnesses beginning by the age of 14.^{1,2} While the exact cause of most mental illnesses is unknown, the interaction between genetic susceptibility and environmental exposures is likely a contributing factor. As emerging evidence links toxicant exposure with central nervous system and behavior changes consistent with disorders ranging from schizophrenia to depression, it will be particularly important to incorporate environmental factors in the study of these diseases to allow for better preventive and therapeutic strategies.

This workshop brings together experts in the fields of psychiatry, fundamental neuroscience, human genetics, immunology, and environmental health sciences to identify common pathways and mechanisms implicated in psychiatric disorders that are potential targets of environmental exposures. NIEHS has organized this conference with the primary goal of establishing key elements of a research agenda to help fill critical knowledge gaps. You will be hearing from a stellar group of experts over the next two days who will walk us through the breadth of basic, epidemiological, and clinical research that is being conducted.

I would like to thank the many people who helped make this meeting possible, especially lead organizers Mady Hornig, Deborah Cory-Slechta, Tomas Guilarte, and Jonathan Hollander. It is a pleasure to welcome NIMH and NIDA staff, including the new NIMH Director Joshua Gordon, to join us in this workshop and lend their insight into this new area for our institute. Finally, I want to thank all session participants and panel members who have generously dedicated many hours of their time to this effort.

It is our hope that this conference will help determine the most appropriate and productive directions for research in the area of environmental factors and risk for mental disorders. Thank you for your active participation.

Linda Birnbaum

Linda Birnbaum, NIEHS Director

¹ Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50).

² Kessler, R.C., et al. (2005). Prevalence, Severity, and Comorbidity of 12-Month DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62(6), 593–602.



National Institute of
Environmental Health Sciences

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AGENDA

DAY ONE – MARCH 21, 2017

- 8:30 – 9:00 a.m. **Registration**
- 9:00 a.m. **Brief Introduction to Workshop**
Jonathan Hollander, *NIEHS*
- 9:15 a.m. **Welcome**
Linda Birnbaum, *NIEHS*
- 9:30 a.m. **Keynote Address One:**
The Architecture of Risk for Psychiatric Disorders: The Implication of Multiple Risk Factors with Small Effects for Future Research
Speaker: John Gilmore, *University of North Carolina at Chapel Hill (UNC)*
- 10:20 a.m. **Session One:**
Genetic Architecture of Psychiatric Disorders: Implications for Environmental Etiologies
Chair: Tomas Guilarte, *Florida International University*
- 10:25 a.m. **Genetic Risk Architecture for Psychiatric Disorders: Update 2017**
Anjene Addington, *National Institute of Mental Health (NIMH)*
- 10:50 a.m. **Integrating GWAS and Epidemiological Data to Accelerate GxE Discovery in Psychiatry**
Jim Crowley, *UNC*
- 11:15 a.m. **Break**
- 11:30 a.m. **Epigenetics as a Potential Mediator and Biomarker in Exposure-Psychiatric Disease Associations**
Christine Ladd-Acosta, *Johns Hopkins University*
- 11:55 a.m. **Cell Type-Specific Mechanisms of Gene-Environment Interaction in Psychotic Disorders**
Mikhail Pletnikov, *Johns Hopkins University*
- 12:20 p.m. **PANEL DISCUSSION**
- 12:50 p.m. **Lunch**

Environmental Risks for Psychiatric Disorders: Exploring Biological Mechanisms



2:05 p.m.

Session Two:

Neuronal Mechanisms and Circuits Underlying Mental Disorder Susceptibility

Following Environmental Exposure

Chair: Deborah Cory-Slechta, *University of Rochester*

2:05 p.m. **Brief Overview of Cellular, Molecular, and Neuronal Mechanisms Commonly Associated With Mental Health Disorders**

Deborah Cory-Slechta, *University of Rochester*

2:15 p.m. **Marijuana Exposure and Schizophrenia Risk**

Beng Choon Ho, *University of Iowa*

2:40 p.m. **Translational Approach to Environmental Contaminants in Psychiatry: Metals in Mice and Human Postmortem Samples**

Steven Szabo, *Duke University*

3:05 p.m. **Early Life Lead Exposure and Schizophrenia: An Environmental Model of NMDA Receptor Hypofunction**

Tomas Guilarte, *Florida International University*

3:30 p.m. **Features of Developmental Exposures to Ambient Ultrafine Particles and Features of Neurodevelopmental Psychiatric Disorders**

Deborah Cory-Slechta, *University of Rochester*

3:55 p.m. **PANEL DISCUSSION**

4:25 p.m.

Day One Summary and Closing Comments

Cindy Lawler, *NIEHS*

4:40 p.m.

Adjourn for the Day

Environmental Risks for Psychiatric Disorders: Exploring Biological Mechanisms



DAY TWO – MARCH 22, 2017

- 8:00 – 8:30 a.m. **Registration**
- 8:30 a.m. **Keynote Address Two:**
Understanding Mental Illness Risk: the NIMH Perspective
Joshua Gordon, *NIMH*
- 9:30 a.m. **Session Three:**
Immune-Inflammatory Signaling and Mental Illness: Role of Environment
Chair: Mady Hornig, *Columbia University*
- 9:30 a.m. **How Chronic Immune Dysregulation Leads to Behavioral Symptoms Among Patients With Mood Disorders?**
Ebrahim Haroon, *Emory University*
- 9:55 a.m. **The Role and Therapeutic Potential of Diet and the Gut Microbiota in Brain and Behavior**
Felice Jacka, *Deakin University*
- 10:20 a.m. **Autoimmunity and Neuropsychiatric Disorders: The Case for Microbial and Xenobiotic Triggers**
Mady Hornig, *Columbia University*
- 10:45 a.m. **Modulation of Microglia by Maternal Immune Activation: Relevance for Neuropsychiatric Disorders**
Staci Bilbo, *Harvard University*
- 11:10 a.m. **PANEL DISCUSSION**
- 11:40 a.m. **Lunch**
- 12:35 p.m. **Session Four:**
Tool and Resource Advances for How to Model Environmental Factors in Psychiatric Disorders
Chair: Cindy Lawler, *NIEHS*
- 12:35 p.m. **Explicating the Environment in the Research Domain Criteria (RDoC) Initiative**
Uma Vaidyanathan, *NIMH*
- 1:00 p.m. **Cognitive, Emotional, and Sensory Function in Adult Zebrafish is Impaired by Developmental Exposure to Drugs and Environmental Toxicants**
Edward Levin, *Duke University*
- 1:25 p.m. **Genes, Environment, and Behavior: Mouse Models of Psychiatric Disorders**
Sheryl Moy, *UNC*
- 1:50 p.m. **The Comparative Toxicogenomics Database: A Tool for Exploring Mechanisms of Environmentally Influenced Psychiatric Disorders**
Carolyn Mattingly, *North Carolina State University*
- 2:15 p.m. **PANEL DISCUSSION**
- 2:45 p.m. **Closing Remarks**
Gwen Collman, *NIEHS*
- 3:00 p.m. **Adjourn**



Abstracts

DAY ONE

Keynote Address One: The Architecture of Risk for Psychiatric Disorders: The Implication of Multiple Risk Factors With Small Effects for Future Research

John Gilmore

University of North Carolina at Chapel Hill

Recent studies of psychiatric disorders have revealed that genetic and environmental risk factors are multiple, interacting, and somewhat non-specific with overall small effect sizes. This complex architecture of risk has made it difficult for recent studies to inform clinical care in a meaningful way. Risk biomarker studies, including imaging, have also not been that helpful in the face of heterogeneous and often overlapping clinical disorders. With a focus on schizophrenia, recent studies of risk will be reviewed and the implications of these studies for future research in post-genomic and post-imaging psychiatry will be discussed. Studies of early brain development in at-risk children will be summarized as one potential approach for dealing with the complexity of risk for psychiatric disorders.

SESSION ONE:

Genetic Architecture of Psychiatric Disorders: Implications for Environmental Etiologies

Anjene Addington

National Institutes of Mental Health

"Genetic Risk Architecture for Psychiatric Disorders: Update 2017"

Since the early 20th century, clinicians noted that mental illness tended to run in families. In the 1950s and 60s, family, twin, and adoption studies all provided robust evidence that the etiology of mental illness harbored a large contribution from heredity. Nevertheless, the paradox remains that though family history is the largest predictor of mental illness, most patients do not have a family member who is ill. The inheritance is complex, comprised of many genes, likely hundreds or evens thousands, which in combination with unknown environmental factors, determine an individual's risk. As genomic technologies have advanced over the past several decades, we are now at a point where we can definitively rule out certain genetic models and must embrace the empirical evidence that the biology has revealed. Through large genome-wide association study (GWAS) efforts that include tens of thousands of individuals, we now know that the genetic risk architecture for mental illnesses is even more complex than ever imagined. Given this knowledge, we must be strategic in how we move forward in pursuing greater insights into the environmental factors, currently largely unknown, that also inevitably contribute to an individual's risk of mental illness.

Jim Crowley

University of North Carolina at Chapel Hill

“Integrating GWAS and Epidemiological Data to Accelerate GxE Discovery in Psychiatry”

Geneticists and epidemiologists have more reason than ever to interact. While we have known for decades that genetic factors influence risk of psychiatric disorders in part by altering sensitivity to environmental factors, it has thus far proven difficult to isolate specific genes and their associated environmental triggers. There are many reasons for this, including misconceptions about GxE interactions, a lack of informative datasets, and the large sample sizes required to detect robust interactions. The aim of this talk is to outline how new developments in genetics and epidemiology can be combined in order to accelerate GxE discovery in psychiatry. We will explore, for example, how to use summary statistics and polygenic risk scores (PRS) from large-scale psychiatric genome-wide association studies (GWAS) to detect GxE interactions in an independent sample. There have also been important advances in statistical methods for GxE detection, including Mendelian randomization, mixed linear models, and pathway-based approaches. Further, just as the costs of genotyping are falling, groups are developing cost-effective and high-throughput ways to assess phenotypes and environmental risk factors. Therefore, we now have improved tools to reach our goal of isolating GxE that can provide etiological insights and perhaps reveal modifiable risk factors that could inform preventive strategies.

Christine Ladd-Acosta

Johns Hopkins Bloomberg School of Public Health

“Epigenetics as a Potential Mediator and Biomarker in Exposure-Psychiatric Disease Associations”

Epigenetics can inform our understanding of environmental risk factors for psychiatric disorders in two, equally impactful, ways. First, since it is reversible, regulates critical cell processes, and enables cells to quickly respond to environmental stimuli without changing the DNA sequence, epigenetic information may provide a biological mechanism for environmental influence on health outcomes. Second, epigenetics can serve as a short- or long-term biomarker of environmental exposure, and thus, may extend our exposure measurement reach for difficult-to-obtain exposures. For both of these purposes, an important first step is to determine whether epigenetic changes are associated with exposures. Therefore, we have begun to evaluate the relationship between DNA methylation (DNAm) profiles in population-based accessible human tissue samples. Examination of 163 cord blood samples revealed a genomic region showing significant differences in DNAm (FWER = 0.028) associated with the amount of prenatal exposure to nitrogen dioxide. Interestingly, there was considerable overlap among the top differentially methylated regions independently identified for nitrogen dioxide and ozone. One of the major challenges to extending our initial exposure-epigenetic findings to psychiatric outcomes is the inability to examine the disease-affected tissue prior to death; this is often referred to as the “tissue issue.” We attempt to address this issue in several ways, including cross-tissue and cross-species analyses; an overview of these approaches and preliminary findings will be presented. Finally, as proof-of-principle support for the potential of DNAm to serve as a biomarker of exposure, we show an epigenetic signature present in peripheral blood samples at age 5 can predict past prenatal exposure to smoking with 81 percent accuracy. Our initial findings suggest epigenetics may provide mechanistic insights into exposure biology and also that it has the potential to serve as an alternative measurement tool for exposures that may not otherwise be available.

Mikhail Pletnikov

Johns Hopkins University

“Cell Type-Specific Mechanisms of Gene-Environment Interaction in Psychotic Disorders”

Environmental risk factors contribute to the pathogenesis of schizophrenia by interacting with genetic risk variants in vulnerable individuals. In order to study the underlying mechanisms of gene-environment interaction (GxE), we exposed genetically engineered mice with inducible expression of mutant Disrupted-In-Schizophrenia 1 (DISC1) in different brain cells to various environmental stressors associated with psychotic disorders, including maternal immune activation (MIA), environmental toxins, or cannabis. We found that mice with neuronal expression of mutant DISC1 and exposed to MIA exhibited neurobehavioral alterations resembling mood disorders, whereas developmental exposure to low doses of Pb2+ produced schizophrenia-like abnormalities treatable with D-serine. Further, chronic adolescent cannabis (tetrahydrocannabinol) exposure of mice expressing mutant DISC1 in neurons exacerbated deficient fear conditioning and synergistically decreased c-Fos expression induced by cue-dependent fear memory retrieval. The same regimen of cannabis exposure in mice expressing mutant DISC1 in astrocytes gave rise to cognitive impairment and decreased number of parvalbumin-positive neurons in the hippocampus of adult mice. These changes were restored in mutant DISC1 mice treated with doxycycline to shut down expression of mutant DISC1 or in mice treated with the COX-2 inhibitor to prevent activation of neuroinflammation in genetically modified astrocytes. Our findings suggest that both common and cell type-specific mechanisms underlie variable clinical presentations of GxE to explain heterogeneity of psychotic disorders.

SESSION TWO:

**Neuronal Mechanisms and Circuits Underlying Mental Disorder Susceptibility
Following Environmental Exposure**

Beng Choon Ho

University of Iowa

“Marijuana Exposure and Schizophrenia Risk”

Schizophrenia, one of the most severe and disabling neuropsychiatric disorders, is a leading cause of global disease burden. As a group, schizophrenia patients show dysfunction involving a variety of neurotransmitter systems and brain circuits. Genetic as well as environmental factors have been implicated in the etiology of schizophrenia. Epidemiologic studies have consistently replicated increased risk for schizophrenia from heavy adolescent marijuana use. Whether this association is causal remains a topic of intense debate. Animal and human studies will be reviewed focusing on the effects of cannabinoids on receptor function, neurotransmission, brain circuits, and in mediating cognition, adolescent brain maturation, outcome in schizophrenia patients, and schizophrenia susceptibility. Using marijuana exposure as a potential environmental risk factor for schizophrenia, the presentation will also illustrate the complexities and challenges associated with identifying critical signaling pathways affected in schizophrenia that may aid in the discovery of new treatment options.

Steven Szabo

Duke University

**“Translational Approach to Environmental Contaminants in Psychiatry:
Metals in Mice and Human Postmortem Samples”**

Clinical appreciation of environmental contaminants in brains of neuropsychiatric patients may lead to greater understanding of pathophysiology and treatments. Exposure to various metals and accumulation is linked to onset and modulation of neuropsychiatric illness. For example, lithium is a mood stabilizer with neuroprotective properties and is a prototypical antimanic agent that reduces protein kinase C (PKC) activation; whereas, trimethyltin (TMT) neurotoxicity mimics symptoms of bipolar disorder and increases PKC signaling.

Animal Studies: Mice (CD-1) receiving a neurotoxic dose of TMT (2.4 mg/kg, i.p.) exhibited enhanced activity in the open field and forced swim test consistent with a manic-like phenotype. Increased open field activity following TMT injection was abolished in mice pretreated with lithium (LiCl 75mg/kg, i.p.). Chronic lithium treated mice exposed to TMT did not display TMT induced passive avoidance learning deficits, and locomotor activity to an amphetamine challenge was increased by approximately 800 percent. Environmental neurotoxicants and psychotropic interactions warrant further investigation, and biomarkers of brain metal levels are needed for clinical translation. Human Studies: Postmortem samples of frontal cortex (FC) and ventricular-cerebral spinal fluid (CSF) were analyzed for 13 metals* using a within-subject design in non-demented elderly controls and Alzheimer’s disease cases (AD) (Szabo et al., 2016, *Toxicol Sci, Apr; 150(2): 292-300*). Metal levels were lower in the CSF as compared to FC (with exception of equivalent lead levels), and the essential metals copper, iron, and zinc were highest. In AD cases, FC levels of iron were higher and levels of arsenic and cadmium were lower, while arsenic levels were higher in the CSF. Clinical severity (i.e., Braak stage) was associated with higher FC iron levels and lower arsenic, manganese, and zinc levels. Appreciating metal levels in brain using CSF could provide an objective measure of clinical severity in patients with neuropsychiatric disease and testing of novel therapeutics.

*arsenic (As), cadmium (Cd), 20 chromium(Cr), cobalt (Co), copper (Cu), iron (Fe), lead (Pb), manganese (Mn), mercury (Hg), nickel (Ni), tin (Sn), vanadium(V), and zinc (Zn)

Tomas Guilarte

Florida International University

“Early Life Lead Exposure and Schizophrenia: An Environmental Model of NMDA Receptor Hypofunction”

Environmental factors have been associated with psychiatric disorders, and recent studies suggest an association between prenatal lead exposure and schizophrenia. Early life lead exposure (ELLE) in a rodent model recapitulates key behavioral and neuropathological findings present in schizophrenia subjects. The glutamatergic hypothesis of schizophrenia posits that hypoactivity of the NMDA receptor (NMDAR) complex plays an important role in the pathophysiology of schizophrenia. Lead is a potent NMDAR antagonist, and exposure in early life alters the ontogeny of NMDAR subunits leading to deficits in synaptic plasticity and cognitive function. Specifically, ELLE arrests the ontogenetic switch of NMDAR subunits from a predominantly NR2B-containing complex in early life to a NR2A subunit NMDAR complex in the adult brain. Thus, lead-exposed adolescent animals exhibit a decreased proportion of the total NMDAR current that is NR2A subunit dependent relative to controls. This finding is relevant to hallmark pathology in schizophrenia since NR2A-containing NMDAR complexes are important for the maintenance of parvalbumin (PV) and glutamate decarboxylase (GAD67) positive GABAergic interneurons, the same neurons that are decreased in the schizophrenia brain and in the brain of lead exposed animals. One functional consequence of the loss of PV+ GABAergic interneurons is hyperactivity of the subcortical dopaminergic system, a hallmark feature of schizophrenia. Lead exposed animals exhibit a significantly higher response to cocaine and have higher levels of striatal dopamine metabolites consistent with a hyperactive subcortical dopaminergic system. Collectively, these findings provide strong evidence that ELLE may be a risk factor for mental disorders and specifically schizophrenia.

[Supported by NIEHS grant number ES006189-22]

Deborah Cory-Slechta

University of Rochester Medical School

“Features of Developmental Exposures to Ambient Ultrafine Particles and Features of Neurodevelopmental Psychiatric Disorders”

Increasing evidence points to the central nervous system as a target of air pollution. Neurodevelopment represents a period of particular vulnerability of the brain given that it encompasses a period during which multiple events must unfold synchronously and precisely and in a differential trajectory by sex. Consequently, disruption of this orchestration can lead to persistent neuropathological, neurochemical, and behavioral deficits. Disruptions such as those produced by maternal inflammation/infection have been suggested to serve as a developmental insult that leads to a schizophrenia-like phenotype. Recent studies from our laboratory suggest that exposures to the concentrated ambient ultrafine particle component of air pollution in mice during the human third trimester equivalent results in characteristics related to schizophrenia. One such feature is enlargement of the lateral ventricle (ventriculomegaly), which was observed in males, but not females, out to at least postnatal day 270. This was accompanied by reductions in the size of the corpus callosum as well as significant reductions in its myelination, suggesting failure of myelination to proceed and/or loss of myelination. In addition, a persistent increase in glutamate was seen in both sexes, but was seen more broadly by region in males and produced a significant excitatory-inhibitory imbalance only in males. Behaviorally, these exposures have resulted in deficits in learning which were male-specific, and impulsive-like behavior only tested as yet in males. Collectively, such findings suggest that air pollution, particularly its ultrafine component, could contribute risk to components of the schizophrenia phenotype as well as to neurodevelopmental/ neuropsychiatric disorders with which it shares features. [Supported by R01 ES025541 and P30 ES001247]

DAY TWO

Keynote Address Two: Understanding Mental Illness Risk: the NIMH Perspective Joshua Gordon

National Institute of Mental Health

A complex web of genetic and environmental factors increase risk for mental illnesses. I will discuss NIMH efforts to understand this risk, including consideration of NIMH priorities, the ECHO program, autism, schizophrenia and PTSD.

SESSION THREE: Immune-Inflammatory Signaling and Mental Illness: Role of Environment

Ebrahim Haroon
Emory University

“How Chronic Immune Dysregulation Leads to Behavioral Symptoms Among Patients With Mood Disorders?”

Dysregulated inflammatory activity is consistently seen in a subgroup of patients with chronic mood disorders and has also been associated with treatment non-responsiveness, neuroprogression, and declining functional/cognitive status among these individuals. We model these neurobehavioral changes as resulting from a selective targeting of underlying behavioral neural circuits by immune molecules to shift behavioral priorities away from an energy-expending life-as-usual to an energy-conserving/self-protective mode to enable healing, repair, and survival. We will present data from our decade-long studies to demonstrate that immune mechanisms accomplish these behavioral effects and neural changes at least in part by modulating glutamate concentrations in the key regions associated with processing affective and cognitive information. We will also illustrate how we developed our experimental model by using a combinatorial approach encompassing multimodal in vivo human neuroimaging protocols, plasma and CSF immune marker profiling, immune-stimulation paradigms, and structured behavioral testing to examine these hypotheses in a sample of mood disordered individuals. We will conclude by providing an objective assessment of the translational relevance, promises, and pitfalls involved in modifying disease trajectories using mechanistic insights based on our findings.

Felice Jacka

Deakin University and University of Melbourne, Australia

“The Role and Therapeutic Potential of Diet and the Gut Microbiota in Brain and Behavior”

With depressive disorders the leading source of disability globally, the identification of new targets for prevention and management is imperative. A rapidly emerging field of research suggests that the microbiome-brain axis is of substantial relevance to mood and behavior. Similarly, unhealthy diet has recently emerged as a significant correlate of and risk factor for depression. This presentation addresses evidence for the gut microbiota as a key factor mediating the link between diet and depressive illness and focuses on the potential of gut-focused interventions for the prevention and treatment of mood disorders.

Recent findings: The development of new technologies is affording a better understanding of how diet influences gut microbiota composition and activity and how this may, in turn, influence depressive illness. New evidence is also pointing to the possible utility of pre and probiotic formulations and fermented food in influencing mental health.

Summary: Although in its early stages, the emerging field of research focused on the human microbiome suggests an important role for the gut microbiota in influencing brain development, behavior, and mood in humans. The recognition that the gut microbiota interacts bi-directionally with other environmental risk factors, such as diet and stress, suggests promise in the development of interventions targeting the gut microbiota for the prevention and treatment of common mental health disorders.

Mady Hornig

Columbia University

“Autonimmunity and Neuropsychiatric Disorders: The Case for Microbial and Xenobiotic Triggers”

Immune disturbances, including the presence of altered levels of soluble immune molecules and autoantibodies that target nervous system antigens, have been identified in subsets of a diverse range of neuropsychiatric disorders and in related animal models. Fetal exposures to disrupted maternal inflammatory and autoimmune phenomena have also been shown to be associated with subsequent diagnoses of neurodevelopmental and other brain conditions. Such adverse consequences likely require a perfect storm at the intersection of genetic and maturational, age-related vulnerabilities with environmental triggers of such immunologic dysregulation. Neuroimmune interplay and cross-talk along the gut-brain axis, with communication by molecules of the inflammasome and metabolome, are vital elements of normal brain development and function across the life course. The microbiome – which can become deranged through exposure to xenobiotics – plays a key role in maintaining healthy neuroimmune responsiveness. While immune mechanisms may be unlikely to explain pathogenesis for the majority of cases of psychiatric illness, immune-mediated subsets may nonetheless represent unique opportunities to reveal the mechanisms by which environmental factors impact upon neuroimmune processes and provide clues for more effective interventions. Prior work has focused on prenatal and early postnatal immune, microbial and xenobiotic challenges in animal models to assist in dissecting the pathogenic mechanisms, including pathways to the production of autoantibodies targeting the brain. Our current work concentrates on delineating microbial and xenobiotic triggers of neuroimmune disruption in a range of neuropsychiatric conditions – from autism to affective disorders, and myalgic encephalomyelitis/chronic fatigue syndrome to age-related cognitive deficits – using immune, metabolomic (exposome) and proteomic approaches and integration with data on the microbiome and infectious and xenobiotic exposures. Advancing knowledge of how prenatal microbial and xenobiotic stimuli shape early and later life brain health through fetal programming, and of the relationships of neuroimmune and metabolic biomarkers to distinct clinical phenotypes of neuropsychiatric disorders, is suggesting novel concepts for prevention and treatment of some subsets of neuropsychiatric illnesses. [Supported by NINDS R56 NS086122 and NIAID R56 AI120724]

Staci Bilbo

Massachusetts General Hospital for Children, Harvard Medical School

“Modulation of Microglia by Maternal Immune Activation: Relevance for Neuropsychiatric Disorders”

There is mounting evidence that microglia are involved in several aspects of brain development and function. Many immune molecules (e.g., interleukin [IL]-1 and CCL2, respectively) are produced by microglia at much higher baseline levels in the developing brain compared to the adult brain, although this time course depends highly on brain region and sex. These collective data have led us to hypothesize that early development represents a sensitive period for immune perturbation and thus long-term alterations in neural function, because the immune system is so active within the brain at this time. Indeed, evidence from both animal and human studies implicates the immune system in a number of disorders with known or suspected developmental origins, including schizophrenia and autism spectrum disorders. We developed a novel model that employs the combined effects of an ethologically relevant maternal stressor and environmentally relevant pollutant, diesel exhaust, both of which increase inflammation and impact microglia, and have been implicated in the increased risk of disorders like autism. We show that maternal diesel exhaust particle (DEP) exposure combined with maternal stress (MS) (but neither in isolation) produces early-life communication and social deficits, and long-term cognitive deficits and strikingly increased anxiety, in male but not female offspring. Notably, DEP exposure significantly alters microglial colonization of the male but not female embryonic brain, and combined prenatal DEP and MS exposure leads to persistent functional changes within toll-like-receptor (TLR) pathways in the microglia of the same brain regions of males. Beyond their functions in innate immune defense of the brain, microglia are important regulators of normal brain development, and thus may present novel targets for intervention or therapy. [Supported by NIMH R01 MH101183 and NIEHS R01 ES025549]

SESSION FOUR:

Tool and Resource Advances for How to Model Environmental Factors in Psychiatric Disorders

Uma Vaidyanathan

National Institute of Mental Health

“Explicating the Environment in the Research Domain Criteria (RDoC) Initiative”

The Research Domain Criteria (RDoC) initiative was launched by the National Institute of Mental Health (NIMH) in 2009 to refocus research efforts on mechanisms associated with mental disorders, away from currently existing diagnostic categories. This talk will cover the background for RDoC, its basic principles, and its operationalization in the form of the RDoC matrix. It will highlight the notion of functional constructs, which form the nexus of the RDoC research framework. It will also go over frequently asked questions and misunderstandings about RDoC – one of which is the role of the environment in the RDoC research framework. While RDoC encourages the study of environmental and neurodevelopmental factors, it does not explicitly specify these to the same degree as other elements such as the constructs and domains. This was a deliberate choice to enable investigators to specify and study the environment in the manner in which they wish in their studies. An additional complication is the issue that while there are some unifying frameworks for studying constructs and domains (e.g., emotion, cognition) that are empirically supported, environmental factors appear to have a less widely accepted common structure. One major aim for the future development of RDoC is to devise optimal strategies for moving forward in this regard.

Edward Levin

Duke University

**“Cognitive, Emotional, and Sensory Function in Adult Zebrafish is Impaired by
Developmental Exposure to Drugs and Environmental Toxicants”**

Psychiatric diseases are syndromes characterized by a spectrum of neurobehavioral impairments including cognitive, emotional, and sensory dysfunctions. The Research Domains criteria (RdoC) paradigm of neuropsychiatric investigation provides a systemization for studying these neurobehavioral dysfunctions that contribute to psychiatric syndromes. These neurobehavioral functions can be readily studied in non-human model organisms to help determine the neural bases of behavioral dysfunction. Mostly rodent models have been used in this regard to gain better basic mechanistic understanding and search for causes and effective treatments of psychiatric diseases such as schizophrenia, depression, anxiety disorder, and other psychiatric illnesses. To facilitate both mechanistic understanding and the search for causes and cures, a simpler higher throughput model could be helpful. Zebrafish have become more widely used in the past decade in studies of biobehavioral development. We and others have developed a variety of validated behavioral tests to assess cognitive, emotional, and sensory function in zebrafish. These tests have been developed with each having internal metrics to ensure their validity. They have been vetted for appropriate responsivity to behavioral and pharmacological manipulations. We have shown that, as in rats, low dose chlorpyrifos exposure of zebrafish during development causes long-term behavioral effects in tests of cognition, emotion, and sensory response. A variety of other drugs and environmental chemicals have also been found to have distinct impacts on this behavioral test battery. Zebrafish models have utility and limitations for measuring neurobehavioral toxicity. In a complementary spectrum of model systems, zebrafish can provide a crucial bridge between high-throughput neural cell culture screening and research intensive complex rodent models.

Sheryl Moy

University of North Carolina at Chapel Hill

“Genes, Environment, and Behavior: Mouse Models of Psychiatric Disorders”

Advances in the field of mouse genetics, including sophisticated techniques for controlled gene expression and engineering of mutant lines, have significantly enhanced the utilization of mouse models for complex human health issues, including detrimental gene x environment interactions in susceptibility for psychiatric disorders. Behavioral analysis has become increasingly important for research with these models, and requires testing regimens that reflect core symptoms of mental illness and neurological conditions, as well as assays for common co-morbidities. As one example, a battery of mouse behavioral tests have been developed to model symptoms related to anxiety and mood in humans, including altered responses to stress and hyper-reactivity to environmental stimuli. Notably, mice exposed to viral or inflammatory agents, such as lipopolysaccharide (LPS), can exhibit long-term exaggeration of startle responses, reflecting persistent disruption of HPA axis function. Behavioral profiles in models of complex psychiatric diseases, such as schizophrenia, can involve multi-domain phenotyping to reflect the diverse symptomatology of clinical cases, including positive and negative symptoms, as well as cognitive deficits. Research with mouse models can be facilitated by large-scale government initiatives, such as the Mutant Mouse Regional Resource Centers and the International Mouse Phenotyping Consortium, which offer resources for the development of new mutant lines relevant to candidate genes for human disorders, and publicly available databases of standardized protocols and murine phenotypes. Overall, mouse behavioral models informed by multi-domain clinical profiles have proven to be valuable tools for the investigation of environmental factors in the etiology of psychiatric disorders.

Carolyn Mattingly

North Carolina State University

**“The Comparative Toxicogenomics Database: A Tool for Exploring Mechanisms
of Environmentally Influenced Psychiatric Disorders”**

The Comparative Toxicogenomics Database (CTD; <http://ctdbase.org>) is a freely available resource that aims to advance understanding about mechanisms underlying environmental exposures and their effects on human health. CTD provides manually curated content from the primary literature in several targeted areas: 1) our core content captures chemical-gene interactions from vertebrates and invertebrates as well as gene-disease and chemical-disease relationships; 2) chemical-phenotype relationships detail chemically influenced changes at the molecular, cellular, physiological, and organismal level across vertebrates and invertebrates that may serve as important biomarkers preceding disease outcomes; and 3) exposure content that captures detailed information about population-based measurements of exposures and associated outcomes. To date, core content in CTD comprises more than 1.6 million interactions for approximately 15,000 chemicals, 43,000 cross-species genes, and 6,500 diseases; chemical-phenotype data comprises more than 80,000 interactions linking 5,200 chemicals to 2,900 biological phenotypes; and exposure content includes information for more than 800 environmental stressors and 510 phenotypes and diseases. These data are also integrated with functional and pathway information from the public domain and analysis tools to inform development of mechanistic hypotheses. Among the many diseases with curated information in CTD, neurological and mental health disorders feature prominently (e.g., more than 80,000 chemical-gene interactions). The integrated data structure of disease and chemical content in CTD allows users to navigate by broad-based or granular classifications (e.g., neurodegenerative diseases vs. Alzheimer’s disease; heavy metals vs. cadmium) to identify unique and overlapping potential mechanisms that may shed light on how the environment influences psychiatric disorders. CTD content and examples will be described.



Biographies

Anjene Addington

National Institute of Mental Health

Anjene Addington, Ph.D., first joined the National Institute of Mental Health (NIMH) as an intramural staff scientist in 2002, where she led the genetics research program in the Child Psychiatry Branch, primarily focusing on the genetics of childhood onset schizophrenia and other severe neurodevelopmental disorders. After a two-year hiatus from the National Institutes of Health (NIH), working as consultant from 2010-2012, Addington rejoined NIMH in the extramural program, administering the Genetics of Mental Illness and Genetic Epidemiology Programs in the Genomics Research Branch. Addington has been serving as the Branch Chief of the Genomics Research Branch in the Division of Neuroscience and Basic Behavioral Science since 2015. In addition, Addington has been heavily involved with a number of key NIH and NIMH efforts, among them the Genotype-Tissue Expression (GTEx) Common Fund program, the whole genome sequencing for psychiatric disorders program (WGSPD), and serving as liaison to other agencies for special initiatives. After receiving her bachelor's degree in psychology from the University of Virginia, Addington conducted research on the molecular genetics of type 2 diabetes as a pre-doctoral research fellow at the National Human Genome Research Institute (NHGRI). Addington received her master of public health and doctorate in genetic epidemiology from the Johns Hopkins Bloomberg School of Public Health.

Staci Bilbo

Harvard University

Staci Bilbo, Ph.D., has been working on the role of immune molecules in both normal and disrupted brain development in preclinical models for the past 13 years. Her interest in this field is based on her training in neuroscience and in immunology, and on the evidence from human and animal studies that immune system dysfunction or inflammation may be critical in a number of neuropsychiatric disorders, including autism. A particular focus of her work is on the resident immune cells of the brain and microglia, including their development and function in response to early-life inflammatory signals. Bilbo developed a model of neonatal bacterial infection during her post-doc and early years as an assistant professor that demonstrated that neonatal infection leads to lifelong vulnerability to cognitive disruption via specific, enduring changes in microglial function (Bilbo et al., *J Neurosci*, 2005; Williamson et al., *J Neurosci*, 2011). Based on these results, Bilbo has argued that the early-life environment of an individual is especially critical in shaping the way that microglia and hence the brain develop, with significant consequences for brain and behavior throughout the remainder of the lifespan. Bilbo further hypothesized this model would provide a reference for the understanding of a potentially wide range of genetic and environmental factors that impact the developing immune system, which thereby enduringly alters neuroinflammatory function, and thus, the risk of disorders such as autism. Bilbo now has strong evidence that this is the case.

Linda Birnbaum

National Institute of Environmental Health Sciences

A board certified toxicologist, Linda Birnbaum, Ph.D., has served as a federal scientist for over 37 years. She has received many awards and recognitions, including the North Carolina Award in Science, the Women in Toxicology Elsevier Mentoring Award, the Society of Toxicology Public Communications Award, EPA's Health Science Achievement Award and Diversity Leadership Award, the National Center for Women's 2012 Health Policy Hero Award, the Breast Cancer Fund Heroes Award, and 14 Science and Technology Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications. Birnbaum was also elected to the Institute of Medicine of the National Academies, and received an honorary degree from Ben-Gurion University in Israel.

Birnbaum is a former president of the Society of Toxicology, the largest professional organization of toxicologists in the world; former chair of the Division of Toxicology at the American Society of Pharmacology and Therapeutics; and former vice president of the American Aging Association. She is the author of more than 800 peer-reviewed publications, book chapters, and reports. She is also an adjunct professor at several universities, including the University of North Carolina at Chapel Hill and Duke University.

A native of New Jersey, Birnbaum received her master's and doctoral degrees in microbiology from the University of Illinois at Urbana-Champaign.

Gwen Collman

National Institute of Environmental Health Sciences

Gwen Collman is director of the NIEHS Division of Extramural Research and Training, where she leads approximately 60 professional staff in areas of scientific program administration, peer review, and the management and administration of about 1,500 active grants each year. She directs scientific activities across the field of environmental health sciences, including basic sciences (i.e., DNA repair, epigenetics, environmental genomics), organ-specific toxicology (i.e., reproductive, neurotoxicology, respiratory), public health related programs (i.e., environmental epidemiology, environmental public health), and training and career development. She also oversees the implementation of the Superfund Research Program and the Worker Training Program.

Prior to her current role, Collman served in program development and management, beginning in 1992 as a member, then as Chief of the Susceptibility and Population Health Branch. During this time, she directed research on the role of genetic and environmental factors on the development of human disease, from animal models of genetic susceptibility to population studies focusing on etiology and intervention. She was responsible for building the NIEHS grant portfolio in environmental and molecular epidemiology, and she developed several complex multidisciplinary research programs. These include the NIEHS Breast Cancer and the Environment Research Centers Program, the NIEHS/EPA Centers for Children's Environmental Health and Disease Prevention, and the Genes, Environment and Health Initiative. In addition, under her guidance, a team created a vision for the Partnerships for Environmental Public Health programs for the next decade.

In recognition of her achievements, she is the recipient of numerous NIEHS Merit Awards, two NIH Director's Awards, and the DHHS Secretary's Award for Distinguished Service. Collman received a doctorate in environmental epidemiology from the University of North Carolina School of Public Health, where she was awarded the 2009 H.A. Tyroler Distinguished Alumni Award.

Deborah Cory-Slechta

University of Rochester Medical School

Deborah Cory-Slechta, Ph.D., is a Professor of Environmental Medicine, Pediatrics and Public Health Sciences at the University of Rochester Medical School, Acting Chair of the Department of Environmental Medicine and principal investigator of its National Institute of Environmental Health Sciences (NIEHS) Core Center Grant. Her research, which includes both animal models and human studies, has focused largely on the behavioral consequences of developmental exposures to environmental chemicals. This work has examined the effects of developmental exposures to metals, pesticides, and air pollutants in animal models and human cohort studies. Current efforts include development of animal models of behavioral toxicology that better simulate the context of the human environment, including assessment of behavioral consequences of the interactions of lead with prenatal stress, and with early behavioral adversity. A newer focus of the laboratory has been on the adverse impacts on the central nervous system of exposures to air pollution during development. These efforts have resulted in over 160 peer-reviewed publications. She previously served as Dean for Research at the University of Rochester Medical School, and as Director of the Environmental and Occupational Health Sciences Institute of Rutgers University. Cory-Slechta has served on advisory panels of the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA), the National Academy of Sciences (NAS), the Institute of Medicine (IOM), and the Agency for Toxic Substances and Disease Registry (ATSDR), as well as on the editorial boards of Environmental Health Perspectives, Neurotoxicology, Toxicology, Toxicological Sciences, Toxicology and Applied Pharmacology, and Neurotoxicology and Teratology. She also served on the EPA Science Advisory Board, the Board of Scientific Counselors at ATSDR, and as Chair of the IOM and NAS Committees.

Jim Crowley

University of North Carolina at Chapel Hill

Jim Crowley, Ph.D., is Assistant Professor in the Departments of Genetics and Psychiatry at the University of North Carolina at Chapel Hill and is affiliated with the Karolinska Institutet, Department of Clinical Neuroscience (Stockholm, Sweden). Crowley's research focuses on psychiatric genomics and includes molecular genetic, epidemiological, and twin studies of obsessive-compulsive disorder (OCD), Tourette syndrome, anorexia nervosa, and schizophrenia. Crowley is principal investigator of two large-scale, National Institute of Mental Health (NIMH) funded international efforts to identify genetic and environmental predictors of OCD and Tourette Syndrome — the Danish OCD and Tourette Study (DOTS), and the Nordic OCD and Related Disorders Consortium (NORDiC).

John Gilmore

University of North Carolina at Chapel Hill

John Gilmore is the Thad and Alice Eure Distinguished Professor and Vice Chair for Research and Scientific Affairs in the Department of Psychiatry at the University of North Carolina at Chapel Hill (UNC). He also directs the UNC Center for Excellence in Community Mental Health and served as President of the North Carolina Psychiatric Association in 2011.

Gilmore received his bachelor's degree in Political and Social Thought from the University of Virginia and his M.D. from the University of North Carolina at Chapel Hill. He did his psychiatry residency at Cornell-New York Hospital and had a psychiatry research fellowship at UNC. He joined the UNC faculty in 1991.

Gilmore has an active research program focused on brain development and risk for schizophrenia. He has about 150 peer-reviewed papers. He pioneered the use of magnetic resonance imaging to study early childhood brain development, and his Early Brain Development Study is following more than 1,000 children longitudinally from birth, the largest study of its kind. Gilmore is also clinically active, specializing in the treatment of schizophrenia and other serious mental illnesses.

Joshua Gordon

National Institute of Mental Health

Joshua Gordon received his M.D./Ph.D. degree at the University of California, San Francisco and completed his psychiatry residency and research fellowship at Columbia University. He joined the Columbia faculty in 2004 as an Assistant Professor in the Department of Psychiatry, where he conducted research, taught residents, and maintained a general psychiatry practice. In September 2016, he became the Director of the National Institute of Mental Health.

Gordon's research focuses on the analysis of neural activity in mice carrying mutations of relevance to psychiatric disease. His lab studies genetic models of these diseases from an integrative neuroscience perspective, focused on understanding how a given disease mutation leads to a behavioral phenotype across multiple levels of analysis. To this end, he employs a range of systems neuroscience techniques, including in vivo anesthetized and awake behaving recordings and optogenetics, which is the use of light to control neural activity. His work has direct relevance to schizophrenia, anxiety disorders, and depression.

Gordon's work has been recognized by several prestigious awards, including the Brain and Behavior Research Foundation – NARSAD Young Investigator Award, the Rising Star Award from the International Mental Health Research Organization, the A.E. Bennett Research Award from the Society of Biological Psychiatry, and the Daniel H. Efron Research Award from the American College of Neuropsychopharmacology.

Tomas Guilarte

Florida International University

Tomas Guilarte, Ph.D., is the dean of the Florida International University (FIU) Robert Stempel College of Public Health and Social Work. He took the helm of FIU Stempel College in January 2016. Guilarte comes to FIU after success as the inaugural Leon Hess Professor and Chairman of the Department of Environmental Health Sciences at Columbia University's Mailman School of Public Health. Before his time at Columbia, Guilarte received his doctorate and spent 30 years as a professor and researcher at the Johns Hopkins University Bloomberg School of Public Health.

A leading scientist, educator, and academic leader, Guilarte's research has focused on determining the role of environmental pollutants on neurological and mental disease. His work uses behavioral, cellular, and molecular approaches, ranging from studies using primary culture of neural cells to the application of brain imaging technologies. He is recognized worldwide for revealing the effects of low-level lead exposure on the central nervous system during development, and subsequently developing strategies to mitigate neurological effects. His research team led in the validation and application of a biomarker of brain injury and inflammation that is now used in preclinical and clinical studies throughout the world.

Ebrahim Haroon

Emory University

Ebrahim Haroon is Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Emory University School of Medicine and is the Associate Director of the Emory Behavioral Immunology Program. His research is focused on neuroimaging, in particular magnetic resonance spectroscopy (MRS) and its relevance to investigating the impact of inflammation on the brain. Haroon was the first person to demonstrate that inflammation affects behavior in part by increasing glutamate concentrations in the brain in key regions that regulate motivation and motor activity. These findings, which have been replicated in two separate models of human depression, have far-reaching implications, including the notion that subpopulations of patients with increased inflammation may preferentially respond to glutamate-targeted treatments. Haroon has also developed a research program in MRS at Emory, and, after obtaining a K23 award, proceeded to obtain two NIH R01 grants for his work. In addition, Haroon has extended his work to cancer, where he is studying the effects of cancer treatment and the associated inflammation on brain glutamate, white matter integrity, and persisting symptoms of depression and cognitive dysfunction that significantly reduce the quality of life in these patients.

Haroon trained in the Department of Psychiatry at Yale University, and subsequently relocated to the University of California, Los Angeles (UCLA), where he trained in MRS with Albert Thomas and Anand Kumar, two of the world's experts in this neuroimaging modality. After being recruited to Emory, Haroon started working with Andrew Miller on the potential impact of inflammation on brain metabolites, including glutamate and myo-inositol, a marker of astrocyte function. Haroon has won a number of awards, including the Walter B. Cannon prize for Physiology in India, the Seymour L. Lustman Research Award at Yale, a Young Investigator Award from the Brain and Behavior Research Foundation (NARSAD), and a new investigator award from the American Society of Clinical Psychopharmacology. Haroon has also served on multiple study sections for the National Institutes of Health, is on the editorial board of Brain Behavior and Immunity, and has served on the Scientific Program Committees of the Society for Biological Psychiatry and the American Society for Clinical Psychopharmacology. Finally, Haroon is double-boarded in Psychiatry and Neurology as well as Brain Injury Medicine.

Beng Choon Ho

University of Iowa

Beng Choon Ho, M.D., focuses on studying schizophrenia pathophysiology and on elucidating neurobiological mechanisms that underlie the etiologic factors, disease susceptibility, phenotypic features, and long-term course of schizophrenia. The research strategy in his work combines multidisciplinary investigative methods so as to maximize scientific discovery regarding the complex syndrome of schizophrenia. The overarching hypothesis unifying his research posits that genetic and environmental factors disrupt the regulation of neural cell signaling and neuroplasticity during sensitive time periods of embryonic and adolescent brain maturation leading to the diverse manifestations of schizophrenia. Ongoing projects include: 1) understanding factors (including cannabis use) affecting brain maturation in adolescent biological relatives of schizophrenia probands using multimodal MR neuroimaging (brain morphometry, fMRI, and diffusion tensor imaging); 2) the role of prenatal maternal immune activation in mediating adolescent brain maturation and schizophrenia susceptibility in the offspring. The long-term goal of his research is to develop and implement evidence-based preventive programs so as to reduce morbidity associated with schizophrenia through early identification and personalized treatment.

Jonathan Hollander

National Institute of Environmental Health Sciences

Jonathan Hollander, Ph.D., is a program director in the Genes, Environment, and Health Branch at NIEHS. Hollander received his doctorate from the Behavioral Neuroscience Program (formerly Biological Program) in the Psychology department at the University of North Carolina at Chapel Hill in 2006. Prior to joining the Division of Extramural Research and Training of the NIEHS, he was a Staff Scientist in the Molecular Therapeutics and Neuroscience Departments at The Scripps Research Institute – Florida. His research background includes the use of genetic, behavioral, electrophysiological, and pharmacological methods to study drug addiction and obesity. As part of a joint fellowship with UNC, Hollander also worked in the Neurotoxicology Branch of the U.S. Environmental Protection Agency (EPA) where he studied the neurodevelopmental effects of polychlorinated biphenyl (PCB) exposure. During his tenure at the EPA, UNC, and Scripps Florida, he was successful in obtaining NIH fellowship and early career awards, and played a key role in developing and implementing new research programs in the aforementioned areas.

Hollander is responsible for basic mechanistic grants in Parkinson's disease and a portion of the neurodevelopmental toxicology portfolio. In addition, he manages grants that focus on applications of brain imaging techniques.

Mady Hornig
Columbia University

Mady Hornig, M.D., is a physician-scientist, board-certified in Psychiatry, and Director of Translational Research at the Center for Infection and Immunity at the Columbia University Mailman School of Public Health, where she is also an associate professor of epidemiology. She did her undergraduate studies as a College Scholar at Cornell, received a Master of Arts in Psychology from The New School for Social Research and her medical degree from Medical College of Pennsylvania, and completed a National Institute of Mental Health/National Research Service Award (NIMH/NRSA) Neuropsychopharmacology Fellowship at Penn. Her research applies a conceptual framework based on gene-environment-timing interactions ("The three strikes hypothesis") to delineate the role of microbial, immune, and toxic factors in the development of brain conditions that manifest across the life course, including autism, attention-deficit/hyperactivity disorder (ADHD), Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS), mood disorders, schizophrenia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and age-related cognitive disorders.

A central objective of her work is to understand how genes and maturational factors interact with microbes and other environmental agents to lead to metabolic disturbances and inflammatory and autoimmune phenomena that disrupt brain development and function, as well as to identify factors that may enhance resiliency to disease. She uses immune profiling, metabolomic, proteomic, epigenetic, and microbiome approaches to uncover markers of disturbed immunity and metabolism that correlate with the clinical deficits underlying complex and disabling Central Nervous System (CNS) diseases such as autism and ME/CFS, applying data from both large, prospective cohort studies and animal models. Her contributions include discovery of functional brain imaging, neurophysiologic, immune, and neuroendocrine biomarkers associated with clinical dysfunction and treatment response in neurodevelopmental disorders, affective illness, psychoses, and ME/CFS, revealing phenotypes with clinical relevance; demonstration in animal models that genetic and maturational factors determine susceptibility to CNS damage after early postnatal xenobiotic exposures; resolution of concerns regarding measles virus in autism using molecular methods; identification of disrupted microbiomes and metabolic and inflammatory machinery in the intestinal tracts of children with autism; and delineation of viral, neuroendocrine, and immune correlates in brain disorders in prospective human cohorts and animal model studies of CNS infection and autoimmunity. Current work is focused on interrogating factors influencing the pathogenesis of immune-mediated neuropsychiatric disorders through exploration of the exposome and inflammasome as proxies for vulnerability to the development of CNS-directed autoimmunity.

Felice Jacka
Deakin University and University of Melbourne, Australia

Felice Jacka, Ph.D., is founder and president of the International Society for Nutritional Psychiatry Research (ISNPR) and president of the Australian Alliance for Prevention of Mental Disorders. She is a National Health and Medical Research Council Career Development Fellow and Principal Research Fellow at Deakin University, Australia, within the School of Medicine, where she heads up the Food and Mood Centre. She also holds Honorary Principal Research Fellow appointments at the Centre for Adolescent Health, Murdoch Children's Research Centre; the University of Melbourne; and the Black Dog Institute in New South Wales. Jacka has pioneered a highly innovative program of research that examines how individuals' diets, and other lifestyle behaviours, interact with the risk for mental health problems. Her current work focuses closely on the links between diet, gut health, and mental and brain health. This research is being carried out with the ultimate goal of developing an evidence-based public health message for the primary prevention of common mental disorders. She has published extensively in high-impact journals in the mental health field, including the American Journal of Psychiatry, World Psychiatry, BMC Medicine, Schizophrenia Bulletin, and Lancet Psychiatry.

Christine Ladd-Acosta

Johns Hopkins Bloomberg School of Public Health

Christine Ladd-Acosta, Ph.D., is currently an Assistant Professor in the Department of Epidemiology at The Johns Hopkins Bloomberg School of Public Health. Her research primarily focuses on integrating genetic, environmental, and epigenetic information to understand autism spectrum and developmental disorders. In addition, she is exploring the potential of epigenetics to serve as a molecular fingerprint, i.e. biomarker, of past exposures. She received her doctorate in 2009 from Johns Hopkins University, where her thesis research focused on epigenomic alterations in cancer. Ladd-Acosta received the Mette Strand Young Investigator Award for her graduate work in which she and her colleagues identified shores as the predominant site of altered DNA methylation in cancer. Prior to that, she was a research technician at the Broad Institute, where she worked to identify gene expression signatures to aid diagnosis, classification, and treatment of human cancers.

Cindy Lawler

National Institute of Environmental Health Sciences

Cindy Lawler, Ph.D., is chief of the Genes, Environment, and Health Branch (GEHB) in the Division of Extramural Research and Training at the National Institute of Environmental Health Sciences (NIEHS). This branch provides programmatic management of research that addresses the fundamental mechanisms by which environmental exposures combine with genetic susceptibility to influence risk of complex human diseases and disorders.

Lawler is the lead NIEHS representative for extramural autism activities. This includes responsibilities as a program official for the NIH-funded Early Autism Risk Longitudinal Investigation (EARLI) study, the Childhood Autism Risk from Genes and Environment (CHARGE) study, the Markers of Autism Risk in Babies-Learning Early Signs (MARBLES) study, and a multidisciplinary center that addresses environmental contributors to autism. In addition to her programmatic role in autism activities, Lawler has primary responsibility for the NIEHS extramural portfolio of Parkinson's disease epidemiology research. Lawler is also leading a strategic team focused on Knowledge Management within the Division of Extramural Research and Training as well as a trans-NIH initiative to support community-based data standards development as part of the NIH Big Data to Knowledge (BD2K) program.

Lawler received her doctorate in experimental psychology at Northeastern University and received postdoctoral training in the Brain and Development Research Center at the University of North Carolina at Chapel Hill (UNC). Prior to joining NIEHS, Lawler was a faculty member in the UNC Department of Psychiatry and in the Program in Toxicology, and held an adjunct appointment in the Department of Biostatistics. She served as a Principal Investigator on an NIH-supported early career research grant in behavioral neuroscience, with an emphasis on dopamine receptor pharmacology and development of novel pharmacologic agents to treat diseases and disorders related to altered dopamine neurotransmission.

Edward Levin

Duke University

Edward Levin, Ph.D., is a Professor of Psychiatry and Behavioral Sciences at Duke University Medical Center. He has secondary appointments in the Department of Pharmacology and Cancer Biology, the Department of Psychology and Neuroscience, and the Nicholas School of the Environment. He directs the Neural and Behavioral Assessment and Training Cores of the Duke University Superfund Research Program and is former Director of the Duke Integrated Toxicology Program. Levin earned his doctorate in Environmental Toxicology in 1984 at the University of Wisconsin. He was a National Institutes of Health (NIH) sponsored post-doctoral fellow in psychopharmacology at the University of California at Los Angeles and was a visiting scientist at Uppsala University in Sweden. Since 1989, he has conducted research and taught at Duke University. Levin's research interests concern the neurobehavioral pharmacology and toxicology. He investigates the neurobehavioral bases of sensorimotor response, addiction, and cognitive function with a focus on the roles nicotinic receptor systems in sensory processing drug abuse, cognitive function, and developmental neurobehavioral toxicology in rats, mice, and zebrafish. He has published over 370 articles and chapters, has edited four books, and has been granted nine patents from over 35 years of research. He is particularly concerned with addiction, and toxicant and therapeutic drug effects on neurobehavioral function, including learning, memory, attention, emotional function, and sensorimotor modulation. His research is directed not only at determining the functional nature and persistence of impairment, but also the mechanisms of dysfunction and the therapeutic treatments to counteract the damage. He has served as president of the Neurobehavioral Teratology Society as well as the Behavioral Toxicology Society. He is co-director of the Duke Center on Addiction and Behavior Change and president of the International Neurotoxicology Society.

Carolyn Mattingly

North Carolina State University

The overarching goal of Carolyn Mattingly's research program is to improve understanding of environmental influences on human health and disease. She uses a multidisciplinary approach involving: a) ongoing expansion of a public database, the [Comparative Toxicogenomics Database \(CTD\)](#), and b) wet bench research using the zebrafish to understand the effects of environmental exposures on human health and development. Since 2001, she has been directing development of CTD, which facilitates understanding about the etiologies of environmentally influenced diseases by providing manually curated chemical-gene interactions, chemical- and gene-disease relationships, and exposure information. These data are integrated with external data sets (e.g., Gene Ontology, pathways), novel analysis tools, and statistical models to predict mechanisms of chemical actions and their impact on health. She is involved in many multidisciplinary and cross-institutional projects that involve re-use of data from CTD, and most recently these have extended to the highly interdisciplinary Big Data to Knowledge program at the National Institutes of Health (NIH). She is also heavily involved in the development and advocacy of standards for environmental health data to improve interoperability and data sharing among the research community. She directs a laboratory that leverages the zebrafish as a model for understanding the mechanisms underlying environmentally influenced toxicity. Endpoints of interest in her laboratory include neurodevelopment and metabolic function. Specifically, her laboratory is conducting both screening and targeted experiments in combination with their many transgenic zebrafish lines to elucidate mechanisms that affect neurodevelopment, neurodegeneration, behavior, and metabolic function in the context of excess lipid storage.

Sheryl Moy

University of North Carolina at Chapel Hill

Sheryl Moy, Ph.D., is a Research Professor in the Department of Psychiatry at the University of North Carolina, Chapel Hill (UNC), and serves as Director of the Mouse Behavioral Phenotyping Laboratory, a core facility of the Carolina Institute for Developmental Disabilities. She received a doctorate in biological psychology, with a focus on behavioral pharmacology, from UNC, and then completed a postdoctoral fellowship in neuropharmacology at the UNC Brain and Development Research Center. Her area of expertise is the development and testing of rodent models for human clinical syndromes, including autism, schizophrenia, and other psychiatric disorders. Current studies in the Moy laboratory utilize knockout or transgenic mouse lines to investigate genetic and environmental risk factors for behavioral abnormalities relevant to human symptoms, such as social deficits, restricted repetitive responses, and cognitive impairment. Moy is also conducting preclinical efficacy studies to evaluate novel oxytocin analogs as treatments for autism-like or schizophrenia-like phenotypes, and has recently initiated a project on the epigenetic basis of prosocial oxytocin effects.

Mikhail Pletnikov

Johns Hopkins University School of Medicine

Mikhail Pletnikov, M.D., Ph.D., is a professor in the Department of Psychiatry at Johns Hopkins University School of Medicine. He received his medical degree in 1986 from I.M. Sechenov Moscow Medical Academy, Moscow, Russia and his doctorate in normal physiology in 1990 from P.K. Anokhin Institute of Normal Physiology, Moscow, Russia. He did his post-doctoral training under Timothy H. Moran (1996-1999) at the Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine and under Kathryn M. Carbone (1996-1999) at the laboratory of pediatric and respiratory viral infections, the Center for Biologics Evaluation and Research (CBER), the U.S. Food and Drug Administration. He joined the faculty of the Johns Hopkins University in 1999. His current research interests focus on understanding pathogenesis of human psychiatric disease with neurodevelopmental origin, e.g., schizophrenia and autism with particular emphasis on a role of gene-environment interactions and the neuro-immune interplay in the complex pathogenesis of psychiatric conditions.

Steven Szabo

Duke University

Steven Szabo, M.D., Ph.D., earned his doctorate in neurosciences from McGill University in 2001. He completed postdoctoral trainings in psychopharmacology at the University of Florida Brain Institute and in the Mood and Anxiety Disorders Program at the National Institutes of Mental Health (NIMH). After medical school and prior to embarking on psychiatry residency training at Duke University in 2009, Szabo participated in the Summers of Discovery Program at the National Institutes of Environmental Health Sciences (NIEHS), Neurotoxicology Group, with a focus on environmental contaminants and mood dysregulation.

As an Assistant Professor and Board Certified Psychiatrist at Duke University, Szabo conducts research in the Division of Translational Neuroscience and Division of Brain Stimulation and Neurophysiology. Szabo is also a member of the Mental Health Service Line and is employed as an Attending Psychiatrist in the Emergency Room at the Durham Veterans Administration Medical Center (VAMC). He is a Mental Illness Research, Education, Clinical Centers of Excellence (MIRECC) workgroup member at the Durham VAMC with special interest in developing and testing biomarkers of mental illness that focus on post-traumatic stress disorders (PTSD) and Gulf War illness. Training as both a neuroscientist and psychiatrist, with his longstanding interest in psychopharmacology, neurotoxicology, and experimental therapeutics, have sculpted this bench-to-bedside approach to research.

Szabo currently conducts fundamental science experiments with both government and industry-funded clinical trials at Duke University and the Durham VAMC. He is an investigator for the NIMH-sponsored Fast-Fail Trials (FAST-MAS), which is a flagship NIMH contract study employing an experimental therapeutic and biomarker approach to early phase treatment studies in patients with mood and anxiety disorders. His passion for validating clinical biomarkers of brain dysfunction using basic science findings from animal and human postmortem samples is representative of his ongoing collaboration with the NIEHS. He has published more than 40 scientific papers in peer-reviewed journals. He also has a passion for psychiatry resident and medical student education and is the course master for Biological Psychiatry at Duke University.

Uma Vaidyanathan

National Institute of Mental Health

As Senior Scientific Program Manager, Uma Vaidyanathan, Ph.D., is responsible for outreach and communications of the Research Domain Criteria (RDoC) Unit. Her research focuses on the structure and correlates of common mental disorders, using EEG and statistical modeling. She has investigated the neurobiology of disorders such as anxiety and depression using the startle blink reflex response. Recently, she has examined a variety of endophenotypes including the P300, startle blink reflex response, antisaccade, resting EEG, and skin conductance in family and twin samples of more than 5,000 subjects, to identify genes associated with such responses. She is also interested in philosophical questions underlying psychopathology.

Vaidyanathan obtained her Ph.D. in biological psychology from the University of Minnesota. She has been at the National Institute of Mental Health (NIMH) since October 2014. Prior to this, she was a Research Associate at the Minnesota Center for Twin and Family Research, where she held a Brain and Behavior Research Foundation (NARSAD) Young Investigator Award to examine brain structure and function in adolescent twins discordant for alcohol use using structural and functional magnetic resonance imaging (MRI).

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